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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
08/803,702	02/21/1997	VERNON C. MAINO	P-3639P1	9092

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EXAMINER
EWOLDT, GERALD R

ART UNIT	PAPER NUMBER
1644	40

DATE MAILED: 12/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/803,702	Maino et al.
Examiner	**Art Unit**
G.R. Ewoldt	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *4/25/02, 7/23/02, and 9/09/02* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *19-24, 26-55, and 61-63* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *19-24, 26-55, and 61-63* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

2. In view of Applicant's responses, filed 4/25/02 and 9/09/02, and the 1.132 declaration of Dr. John D. Altman, filed 4/25/02, upon reconsideration, the previous rejections under 35 U.S.C. 103(a) have been withdrawn.

3. In view of the withdrawal of all art rejections, all claims drawn to non-elected species have been rejoined. Accordingly, Claims 19-24, 26-55, and 61-63 are under examination.

4. Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

5. New corrected drawings must be filed with the changes incorporated therein. See the PTO Form 948, mailed 3/27/00. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the

"Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections. Note that the filing of corrected drawings may no longer be held in abeyance until such time as claims are found allowable. Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 19-21, 23, 24, 26-33, 40, 43, 45, 47, 49-55, and 61-63, and newly rejoined Claims 22, 34-38, 41, 42, 44, 46, 48, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons set forth in Papers No. 24, 28, and 33, mailed 1/30/01, 8/31/01, and 2/26/02, respectively.

Applicant's arguments, filed 9/09/02, have been fully considered but they are not persuasive. Applicant argues that "In the present methods, an inhibitor of cytokine secretion is used in a manner that is auxiliary to the invention. Its function is to allow intracellular cytokines to accumulate. It is unimportant which inhibitor is used to inhibit cytokine

secretion, so long as cytokine secretion is inhibited. The specification provides literal written description of the generic use of an inhibitor of cytokine secretion." It is the Examiner's position that the inhibitor of the claims is neither auxiliary nor unimportant. In fact, the use of an inhibitor comprises a critical element of the claimed method (see paragraph 7, below). More important to the instant rejection is what sort of inhibitors are encompassed by the claims. The specification discloses that, "cytokine detection is enhanced when an agent which blocks the secretion of such intracellular cytokines is added during the activation (4h) period of incubation." It would seem that any agent that could block the secretion of a protein from a cell (as cytokines are proteins) might be encompassed by the claims. The prior art teaches that agents ranging from azide to nicodazole can be considered inhibitors of protein secretion. See for example, Elkeles et al. (1994) which refers to azide as "a specific inhibitor of protein export," or Robin et al. (1995) which teaches that nicodazole can inhibit protein secretion in some instances.

Applicant argues, "The art of record shows that one of skill in the art would construe the genus of cytokine secretion inhibitors, in the context of intracellular cytokine assays, to comprise two agents, monensin and BFA, and that these inhibitors of cytokine secretion were known in the art." It is the Examiner's position that no such constraint as to context, as asserted by Applicant, exists. Any agent capable of inhibiting cytokine secretion, conceivably including any toxin or proliferation inhibitor, such as chloroquine, cytochalasin, bafilomycin, or vincristine, etc., might be encompassed by the claims.

Thus, Applicant's argument that, "It also is well established that there are situations wherein one species adequately supports a genus, particularly where, as in the present case, the genus is used in a manner auxiliary to the invention," is irrelevant, as the claimed genus comprises more than just the two agents monensin and BFA. and improper, as the use of the aforementioned inhibitor is not auxiliary. Accordingly, it remains the Examiner's position that the claimed genus has not been adequately described.

8. Claims 19-24, 26-55, and 61-63 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Elements critical or essential to the practice of the invention, but not included in the claims are not enabled by the disclosure. The instant claims recite a method of detecting

individual T cells that respond to a specific antigen by flow cytometry. As the percentage of T cells that respond to any particular antigen is very small, the specification discloses that the ability to detect said response is highly dependent on several critical factors (see particularly Example 4 of the specification). In addition, Applicant has argued that said detection ability is highly unexpected (see declarations of Drs. Altman and Prussin), thus, said detection ability must be considered to be absolutely dependent of the limitations set forth in the specification. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

At page 4, the specification discloses, "At its simplest, the methodology involves a step process, which involves culturing with the antigen specific stimulus and analyzing an aliquot of the cultured sample for expression of one or more intracellular cytokines and/or early activation antigens in combination with one or more T-cell markers." Clearly then, *at its simplest*, the specification discloses that the claimed method requires *in vitro* antigen stimulation and culture; note that the culture step is not a claimed limitation. Further note that it is well-established that antigen stimulation in the absence of costimulation will result in anergy (not activation), thus costimulation (as recited in Claim 20) must comprise a limitation of independent Claim 19. Example 4 discloses additional required steps. For example, it is disclosed that a maximal response depended critically on the method being performed in slant tubes due to the geometry of the T cell/accessory cell interaction. The Example also discloses that the detection method of the instant claims also depended on "the inclusion of CD69 (not just any activation marker) assessment in the multiparameter protocol." Additionally, the Example discloses that the analysis "requires" the collection of at least 50,000 events. Most importantly, the specification and the post-filing art disclose/teach that the inclusion of an inhibitor of cytokine secretion is essential to the success of the claimed assay. Note that the inhibitor of cytokine secretion, BFA is used in all of the examples in the specification. Further note that, while BFA and monensin might be considered related, post-filing teachings indicate that in assays similar to those encompassed by the instant claims, the effects of the inhibitors are not identical, and the inhibitors should not be considered interchangeable. See for example, O'Neill-Andersen et al. wherein functional differences between monensin and BFA are examined. Note that the reference teaches, "A key aspect of intracellular cytokine detection is trapping the cytokine within the cell," and "We conclude that the choice of a protein transport inhibitor is an

important variable in this assay." Thus, it would appear that these investigators did not find inhibitors of cytokine release to be "auxiliary to the invention" (as argued by Applicant), nor did they find it "unimportant which inhibitor is used to inhibit cytokine secretion, so long as cytokine secretion is inhibited," (also argued by Applicant).

Applicant is advised that, while some of the claims recite some of the aforementioned critical limitations, none of the claims recite all of them. Given the highly unexpected nature of the claimed invention, it would seem obvious that to pick and choose which steps to perform and which steps to leave out, e.g., perform the assay in slant tubes without the use of an inhibitor of cytokine secretion, would render highly unpredictable results. Given said unpredictable results, the method of the instant claims would require undue experimentation, and is thus, not enabled as claimed.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321c may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-24, 26-55, and 61-63 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-37 and 39-40 of copending Application No. 09/526,253. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims drawn to a method of detecting antigen-specific lymphocytes comprising flow cytometrically detecting a cytokine and a T cell subset in the

presence of a protein synthesis inhibitor. Note that at the time of the restriction of the '702 application the claims of said application were drawn to a method of detecting antigen-specific cytokine production. Subsequent amendment of the claims of the '702 application has necessitated this rejection. Further note that the claims of the '702 application are drawn to "an MHC-dependent nominal antigen" while the claims of the '253 application are drawn to a "vaccine antigen". However, neither antigen is defined in the specifications and said antigens are not considered to be patentably distinct. Other dependent claims of both applications recite various combinations of costimulation antigens, cytokines, and accessory molecules such as chelators and fluorophores.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This rejection has not been traversed.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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November 26, 2002

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